

PATENTTI- JA REKISTERIHALLITUS
NATIONAL BOARD OF PATENTS AND REGISTRATION

Helsinki 4.8.2004

REC'D 10 SEP 2004

WIPO PCT

ETUOIKEUSTODISTUS
PRIORITY DOCUMENT



Hakija
Applicant

BCI Bioabsorbable Concepts Oy
Tampere

Patenttihakemus nro
Patent application no

20031090

Tekemispäivä
Filing date

17.07.2003

Kansainvälinen luokka
International class

A61L

Keksinnön nimitys
Title of invention

"Synthetic, bioabsorbable polymer materials and implants"
(Synteettiset bioabsorboituvat polymeerimateriaalit ja implantit)

Täten todistetaan, että oheiset asiakirjat ovat tarkkoja jäljennöksiä Patentti- ja rekisterihallitukselle alkuaan annetuista selityksestä, patenttivaatimuksista, tiivistelmästä ja piirustuksista.

This is to certify that the annexed documents are true copies of the description, claims, abstract and drawings originally filed with the Finnish Patent Office.


Pirjo Kalla
Tutkimussihteeri

**PRIORITY
DOCUMENT**

SUBMITTED OR TRANSMITTED IN
COMPLIANCE WITH RULE 17.1(a) OR (b)

Maksu 50 €
Fee 50 EUR

Maksu perustuu kauppa- ja teollisuusministeriön antamaan asetukseen 1027/2001 Patentti- ja rekisterihallituksen maksullisista suoritteista muutoksineen.

The fee is based on the Decree with amendments of the Ministry of Trade and Industry No. 1027/2001 concerning the chargeable services of the National Board of Patents and Registration of Finland.

Osoite: Arkadiankatu 6 A Puhelin: 09 6939 500
P.O.Box 1160 Telephone: + 358 9 6939 500
FIN-00101 Helsinki, FINLAND

Telefax: 09 6939 5328
Telefax: + 358 9 6939 5328

BEST AVAILABLE COPY

Synthetic, bioabsorbable polymer materials and implants

FIELD OF THE INVENTION

5

The invention relates to synthetic, bioabsorbable polymer materials and implants, like fibres, sutures, meshes and other tissue management, wound closure or tissue engineering device. The invention also relates to methods of preventing and treating infections by using synthetic, bioabsorbable polymer materials and implants, like fibres, sutures, meshes and other tissue management, wound closure or tissue engineering devices.

BACKGROUND OF THE INVENTION

15

Wounds (soft or hard tissue) are basically classified from the surgical point of view into:

- a. clean
- b. clean contaminated
- 20 c. contaminated
- d. dirty
- e. infected

Antibiotic administration is indicated as therapeutic measure for established infection and as prophylactic measure in cases where infection is anticipated, expected or is a potential risk.

Surgery, in general, however, surgeon is careful leads to some degree of devitalization and temporary de-vascularization, with various degrees of haematoma formation. These factors combined with the metabolic response to surgery or injury, with suppressed immunity in

2

surgical or trauma patients, etc, provide a good basis for development of infection in the surgical wounds. In addition, the increased use of implants (sutures being the commonest, susceptibility to infection is increased due to also a combination of factors, e.g. reduced dos of infective bacteria that is needed otherwise to cause infection in healthy patients, susceptibility of implants to bacterial attachment, etc. Bacterial attachment in many of the common infection causative bacteria are associated with biofilm formation which occurs very early in the onset of events in the evolution of infection. Biofilm has probably evolved as a collaborative community of bacteria try to enhance chances of their survival. Hence, planktonic bacteria once attached, most of them produces glycocalyx and a community of bacteria gets surrounded with this protective structure. Macrophages can not affect the bacteria, rather they are frustrated and their released cytokines may further complicate local tissue injury. Antibodies can not also get access to bacteria hiding under the glycocalyx. Antibiotic may be needed in manifold doses to produce their antibacterial effect as they would do with planktonic bacteria. In addition, antibiotic activity suffers due many factors. While it is mandatory to treat infection, the presence of implant and biofilm renders therapy ineffective without its removal, a procedure that must be undertaken to eradicate such a surgical infection. This leads to consumption of time and costs as well as raising the risks of morbidity and mortality in surgical and trauma patients. It would be wise accordingly, rather to prevent bacteria from attachment and glycocalyx formation from the start.

With the invention of synthetic sutures (Dexon^R) in 1969 and its wide clinical acceptance, Vicryl^R has followed in 1974 and both gained wide acceptance and are in daily clinical use. Others, such as Maxon^R, PDS have been also developed. Most of developments focused on

manipulating the initial strength and strength retention properties, handling properties, etc. Monofilamentous sutures have been long considered to be associated with lower rate of infection as compared to multifilamentous ones. Explanations for this observation have been presented in the literature, such as capillary effect, ductility etc.

Knot characteristics (holding) is however, better with multifilamentous, but it has been always the responsibility of surgeon to balance risks and benefits and make the right decision with the choices made, including the type of suture selected for each defined procedure.

In our recent work with ciprofloxacin-releasing PLGA 80/20 granules, we have found that bacterial attachment and biofilm formation is reduced with these materials as compared with control materials (not containing ciprofloxacin or titanium). Ciprofloxacin screws were associated with clear inhibition area of about 30 mm diameter, when incubated in agar plates containing *S. epidermidis*, as compared to 0 mm with controls.

Thus the suture of the present invention will have an obvious impact on the success and outcome of surgery in different fields, and areas from the top to bottom of the body. It will have both industrial and clinical benefits.

One example, can be the use in abdominal surgery and trauma management where commensals may contaminate the wound. Lowered rate of infection, more invasive and early treatment would be contemplated by surgeons, such as in cases of trauma. Such a policy would be otherwise impossible with the current types of suture available to surgeons. One could think of early intervention to

undertake operative rather than conservative management because of more confidence in the type of implant used. This will consequently lead to increased number of cases that can be managed using this novel implant. More lives can be saved and complications reduced.

5

In one example, soft tissue wounds with delayed-presentation, where the potential of infection is increased, though infection can not be established as a diagnosis at the time of presentation, can be managed more effectively and appropriately. In cases where vascularity is compromised such as in the increasing number of patients suffering from peripheral vascular diseases, the importance of raised local concentration of antibiotic, just to where it should be and the time has to be there, will have a clear benefit using this type of implant, the subject of the current invention. Using a suture with antibacterial properties will increase chances of the body to prevent bacteria from developing from a status of contamination into a status of infection.

10
15
20

In one example, amputation, due to traumatic or vascular reasons, the susceptibility to infection can be reduced by fighting bacteria locally where antibiotics administered systemically may not always achieve sufficient concentrations in local tissue environment with compromised vascularity.

25

In one example, the operations of cholecystectomy, GI anastomoses, and urology can be performed with increased safety.

30

US patent No. 4,853,225 describes a method of combating infection in patients, where a medicament depot is implanted in the patient. The medicament depot consists of a physiologically acceptable excipient, which achieves a delayed release.

Polymeric drug delivery implants for treatment of infection of the bone have been developed.

- 5 Surgical devices prepared from extruded materials include mesh prostheses conventionally used to repair hernias. Such mesh fabric prostheses are also used in other surgical procedures, including the repair of anatomical defects of the abdominal wall, diaphragm, and body walls, correction of defects in the genitourinary system, and repair
10 of traumatically damaged organs such as the spleen, liver or kidney or in inducing the formation of fibrous tissue small joint in fingers of rheumatoid patients (U.S. Pat. No. 6,113,640) or as scaffolds for tissue engineering (Galssmaer et al. 2002, Länsman et al. 2002). Mesh fabrics for use in connection with hernia repairs are disclosed in U.S.
15 Patent Nos. 5,292,328; 4,769,038 and 2,671,444. Knitted and woven fabrics constructed from a variety of synthetic fibers and the use of the fabrics, in surgical repair are also discussed in U.S. Patent Nos. 3,054,406; 3,124,136; 4,193,137; 4,347,847; 4,452,245; 4,520,821; 4,633,873; 4,652,264; 4,655,221; 4,838,884; 5,002,551; and European
20 Patent No. 334,046.

Surgical devices prepared from extruded filaments also include mono- and multi-filament sutures (e.g. Kangas et al. J Biomed Mater Res. 2001, 58(1): 121-6, Mäkelä et al. Biomaterials 2002, 23(12): 2587-92,
25 US Pat 4,557,264, 4,911,165, U.S. Patents 6,350,284 and 6,398,814).

It is important during the healing process and subsequent thereto that the surgical devices placed within the body do have pharmacological action in addition to their primary function as tissue management
30 devices. Most importantly, such devices should resist the attachment

6

and growth of bacteria, as well as biofilm formation on or immediately about them. The other important function of surgical devices can be the function of releasing analgesic drugs to provide analgesia to the patient postoperatively. Devices that utilize anti-microbial agents applied to their surfaces such as sutures coated with germicidal ions disclosed in US Pat. 3,642,003 and 3,862,304. Devices, e.g. sutures, comprising coatings of antimicrobial agents are disclosed in US Pat. 5,019,096. Substrates made from filaments, which substrates then are impregnated with an anti-microbial agent are disclosed in US Pat 5,534,288. The antimicrobial agent is said to flow into the interstices between the filaments from which the substrate is formed. It can be more advantageous if multifunctional surgical devices, used for either soft or hard tissue management devices, e.g. as sutures, mesh, etc., prepared from materials that could be made to contain pharmacological agents such as, but not limited to, anti-bacterial, analgesic, or anti-inflammatory agents without coating and/or impregnation processes such as those discussed in the patents above.

Previously-made sutures such as the commercially available Maxon® and PDS®, although have good strength properties, when they were tested for their tensile strength retention in comparison to sutures that we have made of PLDLA and PLLA, more prolonged strength retention was seen with PLDLA or PLLA (Mäkelä et al. Biomaterials 2002, 23(12): 2587-92 and Kangas et al. J Biomed Mater Res. 2001, 58(1): 121-6). These offer more secure and ensured support and reduced risk of failure especially in mechanically demanding repair where the wound is exposed to continuous distraction forces such as that of tendons, ligaments, or abdominal wall, e.g. hernial mesh repair or following trauma/infection (Kangas et al. J Biomed Mater Res. 2001, 58(1): 121-6).

However, without antibacterial properties, surfaces of polymers remain prone to bacterial attachment and biofilm formation, that is difficult to eradicate.

5

Previous patents disclosed bioabsorbable or non-bioabsorbable materials to contain antimicrobial materials, e.g. polypropylene (EP 1157708 A2).

10 Biostable (non-bioabsorbable) materials entail their permanent residence in tissues or need for removal. This automatically is associated with other risks such as that of extrusion, migration, etc and problems which are known in the field of implantology. The use of bioabsorbable sutures may not always provide sufficient support for
15 required prolonged periods of time. A bioabsorbable filament that combines the properties of bioabsorbable materials (eliminated from the body) and non-bioabsorbable materials (prolonged support) may be obtained by using the patented manufacturing technique of SR (US Pat. No ...), such as demonstrated in our experiment (Mäkelä et al. Biomaterials 2002, 23(12): 2587-92). SR-PLDLA monofilaments were
20 found to retain their strength more than Maxon® and PDS®. Compounding PLDLA 70/30 material with ciprofloxacin was found to significantly reduce bacterial attachment, growth and biofilm formation on their surface (See example 1).

25

The use of polymeric carriers in formulations of therapeutic drug delivery systems has gained widespread application, due to their advantage of being biodegradable and biocompatible.

30

SUMMARY OF THE INVENTION

The present invention discloses a novel, synthetic bioabsorbable multifunctional surgical devices that are appropriate for use to mend, repair or treat wounds that are contaminated, infected or at increased risk of infection, due whatever reason, or where infection consequences would be disastrous, should infection supervene. The multifunctional implant of this invention comprises: 1) a synthetic bioabsorbable polymeric (polymer, copolymer or polymer alloy (carrier into which dispersed, mixed, dissolved, homogenized, and/or covalently bound ("dispersed"); 2) an antibiotic or antibiotic mixture, effective for the prevention and/or of infection such as in infected wounds or wound with potential risk of infection or should infection occur, consequences would be catastrophic, such as trauma wounds and wounds breaching natural barriers of heavily-contaminated environment, such as the colon; 3) a additive/coating that can facilitate the function and handling of the material as suture, e.g. to improve knot making and knot holding or its biocompatibility or its visibility, e.g. quinone. The multifunctional device of the present invention can be in any appropriate form into which the polymer matrix, including antibiotic(s) can be formed with the polymer technological processing methods, which contain: a) a bioabsorbable polymer, copolymer or polymer alloy ("polymeric") matrix; b) an antibiotic (antibacterial) and/or anti-inflammatory and/or healing promoting agent or mixture of, dispersed in the matrix, and c) optionally additive agent to facilitate device recognition and/or handling. To put it more precisely, the device according to the present invention is primarily characterised in that it has oriented structure where mixing-orientation induces the production of oval and/or spindle-shaped cavities resulting from initially rounded holes resulting from the inclusion of the particles of the additive agent.

9

According to an advantageous embodiment of the present invention the device is primarily characterised in that

It comprises:

- a synthetic bioabsorbable polymeric matrix, and
 - 5 - an additive phase dispersed into said polymeric matrix,
- wherein the device has reduced modulus and increased elasticity.

In particular, the multifunctional devices of the present invention can be used for: 1) approximation of wound edges (wound closure) to promote
10 healing; and 2) releasing antibiotic to prevent bacterial attachment, proliferation and biofilm formation and consequently prevent infection.

An advantage of the multifunctional bioabsorbable devices of the present invention is that they can be used in the management of
15 wounds (including fractures) and incisions (including (osteotomies) in patients who have a high risk of developing postoperative infections, such as immunocompromised patients whether due to congenital or acquired reasons. Examples include diabetic patients, patients on dialysis, patients on steroids. Patients with compromised circulation
20 either due to trauma or disease may also very well benefit from using the devices of the present invention in combating against infection or at least bringing the risk of down, which would be otherwise impossible to achieve with conventional corresponding devices, without using extra measures such as the administration of antibiotics as a separate
25 procedure or measure.

Provided herein are also methods for forming the multifunctional bioabsorbable devices of the present invention and methods of using the same.

30

10

DESCRIPTION OF THE DRAWINGS

In the following, the present invention will be described in more detail with reference to the figures, in which

5

Fig. 1 is a schematic illustration of the structure of the device of the present invention following mixing and following orientation,

10 Fig. 2 is a schematic illustration of the cavitation effect of the drawing procedure,

Fig. 3 is a schematic illustration of the mesh structure of the device of the present invention, and

15

Fig. 4 is a schematic illustration of the braid structure of the device of the present invention.

20 **DETAILED DESCRIPTION OF THE INVENTION**

Multifunctional devices and implants of the present invention are fabricated to comprise: 1) a synthetic bioabsorbable polymeric (a polymer, a copolymer or polymer alloy) matrix; 2) an antibiotic phase
25 (preferably 1 to 20 w/w%) dispersed into the polymeric matrix, and 3) additive to facilitate the function or handling properties or outcome of use such as coating with wax, using a quinone dye to render it visible in the blood and tissues (surgical field), growth factors to accelerate healing, or anticancer drugs when used in cancer patients, or the like.

30

11

In the preferred embodiment of the present invention, the devices should have a surface that is not favourable for bacteria, yet does not interfere with wound healing to the extent that affects clinical outcome adversely.

5

The multifunctional devices of the present invention can be made in any appropriate form to contain a polymer matrix, antibiotic(s) employing polymer technological processing methods. Typical forms are mono- and/or multifilamentous sutures and their derivatives such as meshes and scaffolds.

10

The bioabsorbable polymeric matrix of the multifunctional devices of the present invention can be selected from a variety of synthetic bioabsorbable polymers, which are described extensively in the literature. Such bioabsorbable, biocompatible polymers, which may release antibiotic(s) over appropriate period of time enough to combat or reduce the risk of infection in defined areas of soft or hard tissue wounds, and which may also act as suitable matrices to include other biomolecules or pharmacological agents or to transplant cells, can include poly- α -hydroxy acids, e.g. polylactides, polyglycolides and their copolymers, polyanhydrides, polyorthoesters, segmented block copolymers of polyethylene glycol and polyterphthalate (Polyactive™), tyrosine derivative polymers or poly(ester amides). Suitable bioabsorbable polymers that can be used in manufacturing of multifunctional devices of the present invention are mentioned in previous patents such as US Pat. No. 4,968,317, US Pat. No. 5,618,563, FI Pat. No. 98136, FI Pat. No. 100217B and in "Biomedical Polymers" edited by S.W. Shalaby, Carl Hanser, Verlag, Munich, Vienna, New York, 1994 and in many other references cited in the above-mentioned publications. Particular polymer that will be used for

20

25

30

12

certain and defined devices will be selected depending on particular indication as governed, e.g. by risk of infection, area of application, type of tissue, vascularity local status and immunological status of the patient, etc. For example, in treating areas with poor vascularity and areas that need prolonged support such as fascial body walls, and tendons a polymer with prolonged strength retention is preferred, such as PLDLA. While when treating a wound with relatively better vascularity in the upper limb or in facial area, or in intestine a faster-to-degrade and faster-to-resorb polymer can be used such as PLGA. Hence polymers will be selected according to intended application and surgical indication.

Variations in the composition of each of the materials used for manufacturing the multifunctional devices of the present invention, such as the molecular weight of the polymer of the matrix, the relative amount of the antibiotic(s) component will affect the rate and amount of antibiotic release, and hence controlling them will allow modifications to be made to have a multifunctional device with controlled release in terms of rate and amount, that can be tailored according to various situations as mentioned above. In general, the lower is the molecular weight of the polymer used, the faster are the biodegradation and drug release.

According to the present invention, multifunctional surgical devices are prepared to have more than one function, i.e. surgical tissue management such as approximation of wound edges, or repair, or fixation of soft tissues such as the skin, muscle, tendon, etc. or hard tissues such as cartilage and/or bone or soft tissue to hard tissue such as ligament to bone. Besides their primary function as surgical devices, they are also intended to confer extended function to the organism, for

13

example but not limited to, combating bacterial attachment, growth and biofilm formation, in one preferred embodiment of this invention, or by supplying analgesia, anti-inflammatory or antipyretic agents in the other preferred embodiment. More than one agent can be added to render
5 the device more efficient, more biocompatible, to have better outcome or more durable or safer function where needed, according to the indication of the implantation.

The device disclosed in the present invention has the pharmacological agent, in preferred embodiment, antibacterial agent dispersed there
10 through (see examples below). The devices are multifunctional in the sense that they provide: 1) tissue management (repair or fixation or *in situ/in vivo/in vitro* tissue management/engineering) in addition to releasing pharmacological agents to make them, e.g. substantially
15 resistant to bacterial attachment, growth and biofilm formation thereon without the need for additional surface treatment of the device, such as coating or impregnation or to the medium or otherwise. In case of infection prophylaxis, supplementary antibiotic doses, can be hence, minimized or eliminated reducing the side effects.

20

An antibacterial agent (antibiotic) is homogeneously dispersed there through in an amount effective to produce multifunctional surgical devices capable of adding a second function, in addition to their primary function of tissue management. As example, but not limited to,
25 preferred embodiment of the present invention, the said multifunctional device can substantially prevent *in situ* attachment, growth of bacteria, and biofilm formation on the surface of such surgical devices or inducing analgesia in the patient. Pharmacological agent dispersed there through, as used herein, includes those materials in which,
30 example is the antibacterial agent dispersed there through, such that

the antibacterial properties of the device include resisting bacterial attachment and growth and/or biofilm formation on the device. Preferred are materials that have already been accepted for use as tissue management devices, for both soft and hard tissues, e.g. sutures, mesh prostheses (soft tissue management or repair), plates, screws or tacks (for hard tissue management such as fixation or regeneration) or for tissue engineering, either as 2D and 3D scaffolds, e.g. U.S. Pat. 6,350,284 and 6,398,814.

- 10 Antibiotic(s) of choice used in these multifunctional devices as one component, to prevent and/or treat infection can be selected from a variety of antibiotics. Antibiotic classes that may the antibiotic of choice, be selected from, comprise, e.g. aminoglycosides, quinolones or β -lactams. Examples include ciprofloxacin, gentamycin, tobramycin, erythromycin, vancomycin, oxacillin, cloxacillin, methicillin, lincomycin, ampicillin, colistin and cephalosporines which are in wide clinical use in all surgical fields. Suitable antibiotics for surgical patients can be found from the standard surgical textbooks.

- 20 A variety of biomolecules that enhance wound healing can also be added.

Coating materials that facilitate handling or colouring dyes that facilitate the discrimination or recognition can also be included.

25

- Several methods for manufacturing multifunctional devices of the present invention are available. Raw material [polymer(s)] and [antibiotic(s)] can be initially in the form of powder, granules, flakes, fibers or other particulate form and can be mixed together mechanically. The resulting mixture can then be heated and processed

15

using the known methods of polymer technology. These include the use of a batch mixer (e.g. Brabender, Banbury, Farrel or Sigmamixer), continuous extrusion process using, e.g. single or twin screw extruder or special conical screw extruder and injection molding, compression molding or ultrasonic compression so that the polymeric matrix melts or softens and the antibiotic phase is dispersed into the polymeric matrix.

In one preferred embodiment of the present invention can be spun into fibres either using melt spinning or with spinning of antibiotic-containing polymer solution. Such fibres can be made into multifunctional devices, sutures in this case, and derived fibre-based fabrics. Such sutures can be used to mend, close or repair wounds of both soft and hard tissues. Such devices are of special importance because of their multifunctionality in: a) promoting healing of wounds by approximating wound edges and reducing haematoma formation and consequently the amount of scar tissue formation, b) act as prophylactic and/or therapeutic antibiotic-releasing system combating against bacterial attachment and biofilm (glycocalyx) formation, c) a third function can be added according to preferred mode of application and specific clinical indication, e.g. in releasing growth factors, anticancer, or analgesic drugs. Such multifunctional devices can be manufactured of matrix polymer(s), and antibiotic(s) and any added third agent that facilitate or adds to improve the functions of the said device, or pellets or granules made of them using polymer processing methods such as continuous compounding extrusion, injection molding compression molding, or pultrusion. Preforms made using the above-mentioned methods can also be oriented and self-reinforced by using solid-state deformation as can be achieved by drawing, shearing, compression, rolling, hydrostatic or ram extrusion.

The device, e.g. sutures or mesh, can be manufactured from bioabsorbable fibers using any of the known methods from mechanical textile and plastics technology. The thickness of the fibers can vary
5 from about 1 micrometer to about 200 micrometers. In preferred embodiment of the invention, the fiber thickness is between ca. 5 micrometers and ca. 150 micrometers.

Structures suitable for making the multifunctional device, wherein the
10 device is a mesh, can be, for example, a cloth, a narrow fabric, a knit, a weave, a braid, or a web. In any of such a case, the structure should be porous with pore size from ca 30 micrometers to ca 1000 micrometers, preferably between ca. 50 micrometers to ca. 400 micrometers. The mesh can be manufactured using one type of fiber,
15 for example PGA or PLA or their copolymeric fibers. It is also possible to make the mesh using two or more different types of fibers depending on the particular application and desired physical characteristics of the implant. A mesh that has both bioabsorbable and non-bioabsorbable fibers can also be made.

20

The said multifunctional device (mesh) can be manufactured by employing known and conventional warp knitting apparatus and techniques, such as the tricot and Raschel knitting machines and procedures described in "Warp Knitting Production" by Dr. S. Raz,
25 Melliand Textilberichte GmbH, Rohrbacher Str. 76, D-6900 Heidelberg, Germany (1987).

The fibers are melt-spun with the 2-screw extruder, where the polymer melt (e.g. at temperatures ranging from 200 degrees to 270 degrees
30 Centigrade) are pressed through e.g. four round die holes having

diameter of e.g. about 0.4 mm. After cooling, filaments are oriented freely in a two-step process at elevated temperature (e.g. 60 degrees to 140 degrees Centigrade) to a draw ratio of e.g. 4 to 8. The final filament diameter can be e.g. 50 micrometers. The filaments were
5 knitted by using a weft-knitting machine, with the fabric having loop size ca. 1 mm.

Following knitting, the mesh is cleaned or scoured, and thereafter annealed to stabilize the fabric. For the latter operation, the mesh can
10 be secured to a tenter frame which maintains the mesh at a predetermined width, the frame then being passed through an elongated heating zone. Following heat setting, the mesh is cut to size, packaged and sterilized.

15 The mesh can be cut to any desired configuration, e.g. a square or rectangular shape of appropriate dimensions. An ultrasonic slitter may be employed to cut the mesh, various types of which are commercially available. Unlike the result one can obtain when cutting with a blade, i.e. frayed yarn ends, or when the yarn ends are heat-sealed, i.e. bead-
20 like formations, cutting the mesh to the desired size.

In case of a multifunctional mesh device having two types of polymers (bioabsorbable and non-bioabsorbable), or purely non-bioabsorbable, the non-bioabsorbable polypropylene monofilament knitted mesh
25 fabricated as described above exhibits good pliability. Depending on the material used to form the mesh, a mesh preferably has adequate flexibility. In addition, depending on the yarn used to form the mesh, a mesh formed preferably has a sufficient burst strength. The PLDLA/PLGA monofilament knitted mesh fabricated as described
30 above.

In a preferred embodiment of the present invention, a mesh that has two different types of filaments is made of bioabsorbable polymer (filament type 1, e.g. PLGA 80/20) that degrades faster than the polymer used for making filament type 2, e.g. PLDLA 70/30 or PLDLA 96/4. Thus, the mesh degrades in two different rates, allowing tissues to develop and replace it in a more controlled and graduated fashion where such an effect is preferred/desired. The slower-to-degrade filaments remain for longer period of time and provide for longer time the desired strength, shape, and protection to treated tissue or tissue defect or damage, while the regenerating tissue gains its strength and density gradually reducing the sudden exposure to load and force, such as in hernia repair and thus, minimising the risks of recurrence, e.g. of hernia. As the filaments degrade away, simultaneously, repair tissue grows to cover the implant parts and detaching from the implant appear particles on top and in between its components (Lämsman et al. 2002), starting from the surface of the implant or its components. The implant resorbs eventually, and is replaced with new repair tissue. Resorption products disappear from the body via metabolic routes. In the end, the tissue defect is filled in by the patient's own regenerated and/or repaired tissue.

As noted in EP 1157708, PLGA 80/20 or PLDLA 70/30 pellets are introduced into an extruder and the extruded material then is drawn to predetermined draw ratios. According to the present invention, the antibacterial agent (antibiotic) is first dispersed throughout the polymer resin in powder form. The resin may be introduced directly into the extruder in powder form, or the resin containing the antibacterial agent may be formed into pellets, which then are introduced into the extruder. The extruded filament, containing pharmacological agent, for example,

but not limited to, antibacterial agent, may be used then to prepare multifunctional surgical devices according to the present invention. Other pharmacological agents or biomolecules that may enhance the function or the multifunctionality of the device may be used employing
5 similar manufacturing techniques.

In view of the process conditions to which the pharmacological agent, e.g. antibiotic may be exposed to unwanted effects, during preparation of the polymer resin, extrusion of the filament and/or yarn and/or rod
10 and/or granules and subsequent production of the multifunctional surgical device itself. The pharmacological agent, in this case, the antibiotic must be selected to withstand being exposed to such manufacturing conditions without undergoing significant loss of its pharmacological, e.g. antibacterial properties. The agent must also be
15 dispersible in the polymer material used to prepare the extruded filaments to make subsequently sutures and meshes, etc.

Antibacterial agents utilized in the present invention may be selected, e.g. from the group synthetic fluoroquinolones. Example antibacterial
20 agent can be, e.g. ciprofloxacin (See example 1 below).

Filaments used to prepare multifunctional devices of the present invention are prepared by extrusion of a polymer material. During manufacture of the device, some of the pharmacological agent, in the
25 preferred example of the present invention is antibiotic, is typically lost due to processing procedure and conditions and/or sterilization but not after storage. The amount of the pharmacological agent, e.g. antibiotic used in preparing the polymer resin is determined based on the amount of agent actually required to be present in the multifunctional
30 device to provide its intended multifunctionality, combined surgical

management and medical therapy. In the preferred embodiment of the present invention, the said pharmacological agent is antibiotic whose containment in the device and subsequent release confers resistance to bacterial attachment, growth and biofilm formation on the surface of the device, taking into account the potential loss of agent due to processing procedures and conditions. The composite material comprises pharmacological agent, e.g. an antibiotic substantially dispersed there through in amounts effective to produce extruded filaments that, in turn, are useful in preparing multifunctional surgical devices that can have additional function such as, but not limited to, antibacterial function in addition to their primary function for tissue repair and management or tissue engineering, substantially preventing *in situ* bacterial attachment, growth or biofilm formation on the surface thereof, etc.

15

The compounding of the pharmacological agent, e.g. antibiotic into the polymer is performed in several steps. The polymer material and the pharmacological agent are fed through a compounding device. Feeding can be accomplished by force, gravity or starve feed systems. The extruder heats and mixes the materials until they are uniformly blended. A twin-screw extruder produces good mixing by forcing the melt back and forth from one screw to the other, thus breaking up flow patterns. The melted compound exits the extruder in strands that are quenched (cooled/crystallized) by water or air and cut into pellets. Those pellets can be then fed into a second extruder where the actual fiber will be manufactured.

25

Accordingly, in such an application example, the composite material must comprise a minimum amount of the antibiotic such that, upon manufacture of the multifunctional surgical device, the said device will

30

be effective to inhibit *in situ*, bacterial attachment, growth, and biofilm formation on its surface. While such multifunctional devices may have trace amounts of bacteria present thereon, the levels of bacteria attached *in situ* will be significantly and will be sufficiently low so as not to lead to (persistent) infection or require addition of antibacterial agents applied to the surface of the device in order to avoid infection, e.g. surface coatings containing anti-microbial agents and significantly lower than traditionally-used implants. The maximum amount of the pharmacological agent that can be used will be limited by the desired properties of specific multifunctional surgical devices. For example, excessive amounts of the agent may over-plasticize or otherwise detrimentally affect the properties of the multifunctional surgical device disclosed in the present invention. Accordingly, the composite material may comprise from about 0.01 to about 50 weight percent of the antibacterial agent, preferably 0.1-30%, based on the total weight of the polymer and the used pharmacological agent. Most preferably, the compound material will comprise from about 1-10 % weight percent of the antibacterial agent. Once having the benefit of the present invention, one skilled in the art will readily ascertain the effective minimum and maximum amounts of the pharmacological agent, e.g. antibiotic.

Self-reinforced multifunctional devices of the present invention are especially important in the sense they can be used in prophylaxis and/or treatment of infection, because the said self-reinforced devices have better strength and strength retention properties than corresponding non-self-reinforced counterparts (Kangas, Mäkelä et al.). Self-reinforcing can render the devices of the present invention more reliable, allows for their wider clinical application.

One type of the multifunctional devices of the present invention can comprise alternating types of fibres (in their multifilamentous structure) that contain different pharmacological agents or biomolecules, e.g. one type of fibre can be an antibiotic-releasing whereas the other growth
5 facto or analgesic or local anesthetic releasing, depending on the clinical indication and site of implantation. The latter can be advantage in more painful operations in their postoperative course, e.g. hernia operations, or in cases of chronic pain such as in cancer patients or in situation should pain occur, it is difficult to manage such may occur in
10 thoracotomy procedures.

The multifunctional device of the present invention can be a part of hybrid device where the said hybrid device contains also non-bioabsorbable fibres or sutures such as may needed for permanent or
15 prolonged support as in the treatment of hernia using techniques such as Leichtenstein's technique. Hernia mesh can be made to have alternating multifunctional bioabsorbable sutures or fibers and non-bioabsorbable ones made into one hybrid devices prepared as mesh or fabric.

20

Following are examples that illustrate further but do not limit the present invention. Modifications of the present invention can be made without departing from the principles of the said invention.

25 EXAMPLES

The following examples illustrate the multifunctional, characteristics of the surgical devices disclosed in the present invention and its preferred embodiment, e.g. characteristics of a PLDLA 70/30, or PLGA 80/20
30 material comprising no antibacterial agent, i.e. a non-multifunctional

device, compared to a corresponding multifunctional device formed from a material comprising about 8% by weight of the active pharmacological agent.

5 **EXAMPLE 1.**

Ciprofloxacin releasing SR-PLGA 80/20 suture

The used additive and pharmaceutically active agent, ciprofloxacin, an antibiotic, was melt-blended in the matrix. The additive agent retained its solid particulate form in the melt-processing temperature of the matrix because of its melting or decomposition temperature higher than the melting temperature of the matrix. The blend was melt-spun into filament, which was drawn. The obtained product and a reference product were subjected to mechanical tests. The product according to the invention showed increased flexibility compared with reference product of the same composition and prepared in the same way but without the inclusion of the additive agent.

CLAIMS

1. A multifunctional synthetic bioabsorbable device, **characterized** in that it has oriented structure where mixing-orientation induces the production of oval and/or spindle-shaped cavities resulting from initially rounded holes resulting from the inclusion of the particles of the additive agent.
2. A multifunctional synthetic bioabsorbable device for wound closure, **characterized** in that it comprises:
- a synthetic bioabsorbable polymeric matrix, and
 - an additive phase dispersed into said polymeric matrix,
- wherein the device has reduced modulus and increased elasticity.
3. A multifunctional synthetic bioabsorbable device, **characterized** in that it has
- physically and chemically non-homogeneous structure,
 - non-homogeneous and homogeneous structure where both effectively and ineffectively using additive dispersed in.
4. A multifunctional synthetic bioabsorbable device, **characterized** in that it has a cavitated spindle-shaped porous structure resulting from mixing-orientation process that increases elasticity and decreases modulus.
5. A multifunctional synthetic bioabsorbable device, **characterized** in that upon having induced cavitation (from mixing-orientation process):
- has increased elasticity

- enhanced drug release
- enhanced tissue ingrowth
- enabled addition of heat-sensitive molecules, e.g. growth factors or modifiers of tissue-reaction

5

6. A multifunctional synthetic bioabsorbable device produced using the said materials and methods that has

- effective processing,
- effective sterilization,
- 10 - effective storage for at least 1-2 years.

7. The multifunctional device of claim 1, **characterized** in that the device is a suture, fiber, thread, cord, wire, or derivatives of these.

15 8. The multifunctional device of claim 7, wherein the device is a mesh.

9. The multifunctional device of claim 8, wherein the device is a mesh comprising alternating absorbable multifunctional fibres of claim 1, and non-bioabsorbable fibres.

20

10. A multifunctional synthetic bioabsorbable device according to any of the claims 1 to 9, **characterized** in that the fibers are either solid or hollow.

25 11. The multifunctional device of claim 7, 8 or 9, wherein the said antibiotic phase comprises 0.01 to 50 % preferably 1-10% of the weight of the said multifunctional device.

30 12. The multifunctional device of claim 7, 8 or 9, wherein the said multifunctional device is monofilamentous in its structure.

13. The multifunctional device of claim 7, 8 or 9, wherein the said multifunctional device is multifilamentous in its structure.

5 14. The multifunctional device of claim 7, 8 or 9, wherein the said multifunctional device has adequate drug releasing rate.

10 15. The multifunctional device of claim 7, 8 or 9, wherein the said multifunctional device has a drug releasing function effective to inhibit bacterial attachment and biofilm formation.

16. The multifunctional device of claim 7, 8 or 9, wherein the said multifunctional device has a good biocompatibility in tissues.

15 17. The multifunctional device of claim 7, 8 or 9, wherein the said multifunctional device has an effective wound closure properties in terms of initial tensile strength, strength retention, knot holding and percentage elongation, improved knot-making and security.

20 18. The multifunctional device of claim 7, 8 or 9, wherein the said multifunctional device has in addition another function of healing promoting agent, anti-inflammatory agent or/and analgesic agent.

25 19. A method of combined wound closure and prophylaxis and/or treatment of surgical infections using the said multifunctional device.

20. The multifunctional device of claim 18, wherein the said multifunctional device has an effective tissue augmentation properties in terms of initial tensile strength, and strength retention.

21. A method of combined tissue management and support as well as prophylaxis and/or treatment of surgical infections using the said multifunctional device of claim 18.

5 22. A method of using the said multifunctional device of claim 18, for combined functions of repair of abdominal wall as well as for prophylaxis and/or treatment of surgical infections.

10 23. The multifunctional device of claim 28, characterized in that the said multifunctional device is comprised of alternating multifilamentous and multifilamentous fibers.

15 24. A method of combined traumatised solid organ enclosure and management as well as prophylaxis against surgical infections using the said multifunctional device of claim 7, 8 or 9.

20 25. The multifunctional device of claim 7, 8 or 9, wherein the device is a tubular organ anastomosis system comprising ring and staples/or tacks.

26. The multifunctional device of claim 7, 8 or 9, characterized in that it is used for the management/ regeneration/repair of

- 25
- body-wall
 - solid organs
 - hollow organs
 - tissues.

27. The multifunctional device of claim 7, 8 or 9, characterized in that it is made by melt or solution processing technique such as

28
compounding with twin-screw extruder and subsequent processing
method such as fiber spinning.

Abstract

The invention relates to methods of preventing and treating infections. More specifically, it relates to the use of synthetic, bioabsorbable polymer materials and implants, like fibres, sutures, meshes and other tissue management, wound closure or tissue engineering devices, which contain: a) a bioabsorbable polymer, copolymer or polymer alloy ("polymeric") matrix; b) an antibiotic (antibacterial) and/or anti-inflammatory and/or healing promoting agent or mixture of, dispersed in the matrix, and c) optionally additive agent to facilitate device recognition and/or handling to facilitate the use and application of finalized product or help to enhance or permit its function. Preferred embodiment of the present invention is a device (suture) that provides a sustained release of antibacterial (antibiotic) over several days to several weeks for the prevention or treatment of infection. The sutures may be effectively implanted into or in the vicinity of: 1) infected tissue, 2) potentially infected tissue, or in tissues where infection, should it occur, its consequences are disastrous.

Fig. 1

44

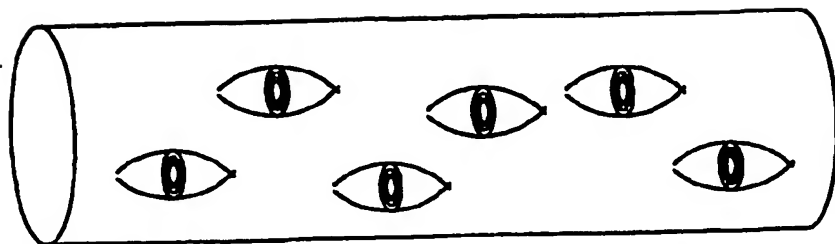


Fig. 1



Fig. 2

14

2

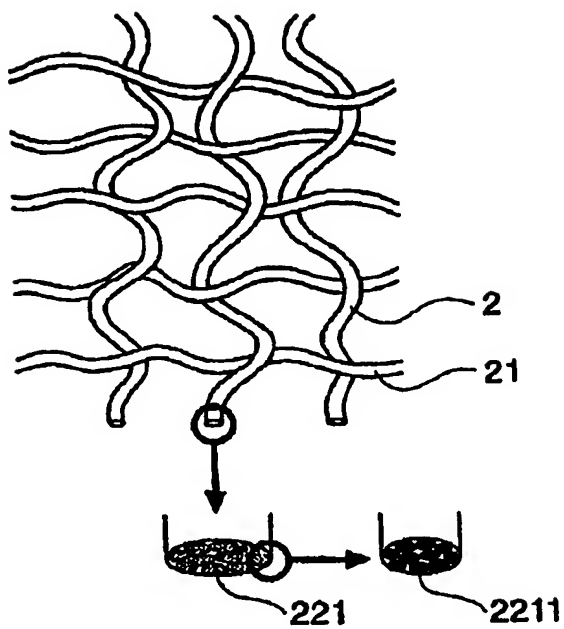


Fig. 3

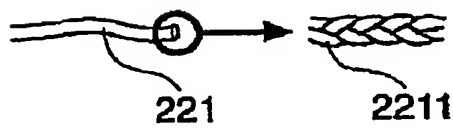


Fig. 4

**This Page is Inserted by IFW Indexing and Scanning
Operations and is not part of the Official Record**

BEST AVAILABLE IMAGES

Defective images within this document are accurate representations of the original documents submitted by the applicant.

Defects in the images include but are not limited to the items checked:

- ☐ BLACK BORDERS
- ☐ IMAGE CUT OFF AT TOP, BOTTOM OR SIDES
- ☒ FADED TEXT OR DRAWING
- ☒ BLURRED OR ILLEGIBLE TEXT OR DRAWING
- ☐ SKEWED/SLANTED IMAGES
- ☐ COLOR OR BLACK AND WHITE PHOTOGRAPHS
- ☐ GRAY SCALE DOCUMENTS
- ☐ LINES OR MARKS ON ORIGINAL DOCUMENT
- ☒ REFERENCE(S) OR EXHIBIT(S) SUBMITTED ARE POOR QUALITY
- ☐ OTHER: _____

IMAGES ARE BEST AVAILABLE COPY.

As rescanning these documents will not correct the image problems checked, please do not report these problems to the IFW Image Problem Mailbox.